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Leukaemia incidence after iodine-131 exposure

PER HALL JOHN D. BOICE, JR GERTRUD BERG
GÖRAN BJELKENGREN ULLA-BRITT ERICSSON ARNE HALLQUIST
MONIKA LIDBERG GÖRAN LUNDELL ANDERS MATTSSON
JAN TENNVALL KERSTIN WIKLUND LARS-ERIK HOLM

Leukaemia is one of the most prominent late effects of exposure to ionising radiation. We have studied the incidence of leukaemia among 46988 Swedish patients exposed to iodine-131 (^{131}I) for diagnostic reasons or to treat hyperthyroidism or thyroid cancer.

The observed number of leukaemias was compared with that expected based on incidence data from the general population. The mean absorbed dose to the bone marrow was estimated as 14 mGy (range 0·1-2·226). 195 leukaemias occurred more than 2 years after exposure, and the standardised incidence ratio (SIR) was 1·09 (95% confidence interval 0·94-1·25). Similar, but again not significantly, increased risks were seen for chronic lymphocytic leukaemia (CLL) (SIR = 1·08), a malignant condition not found to be increased after irradiation, and for non-CLL (SIR = 1·09). The risk of leukaemia did not vary by sex, age, time, or radiation dose from ^{131}I.

One reason for the absence of a radiation effect, other than chance, includes the possible lowering of risk when exposure is protracted over time as occurs with ^{131}I. Excess leukaemia risks of more than 25% could thus be excluded with high assurance in this population of mainly adults These results should be reassuring to patients exposed to ^{131}I in medical practice and to most individuals exposed to the fall-out from the Chernobyl accident.

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Introduction

The induction of leukaemia by ionising radiation has been well documented in man and in laboratory animals.[1,2] The accident at Chernobyl in 1986 has focused further attention on the carcinogenic effect of radioisotopes such as iodine-131 (^{131}I). Recent estimates of leukaemia risk are much higher than those made just 10 years ago but are based almost entirely on populations exposed briefly to ionising radiation at high dose rates.[1] It is unclear whether exposure spread over rime results in lower risk than acute exposure of the same total dose.

Since the physical half-life of ^{131}I is 8 days, the radiation dose is delivered to tissue gradually over time. A "dose-rate effectiveness factor" to reduce the risk coefficient for widely spaced exposure has been suggested by some authorities,[12] one recommendation being a factor of 2.[3] Previous studies of populations exposed to ^{131}I have provided little evidence of leukaemogenesis. [4-10] However, major problems with these

ADDRESSES. **Department of General Oncology** (P. Hall, MD, G. Lundell M D), **Oncological Centre** (A. Mattsson, BA), **Department of Cancer Epidemiology** (K. Wiklund, PhD), **end Department of Cancer Prevention** (L.E. Helm, MD), **Radiumhemmet, Karolinska Hospital, S-10401 Stockholm, Sweden; Department of Hospital Physics, South Hospital, Stockholm** (M. Lidberg, MSc); **Epidemiology and Biostatistics Program. Division of Cancer Etiology, National Cancer Institute. Bethesda, Maryland, USA** (J. D. Boice, Jr, SCD): **Department of General Oncology, Sahlgren's Hospital. Gothenburg** (G Berg. MD); **Department of General Oncology** (G. Bjelkengren, MD) **and Department of Internal Medicine** (U.B. Ericsson. MD), **Malmö General Hospital; Department of General Oncology, University Hospital. Umeá** (A Hallquist, MD); **and Department of General Oncology, University Hospital, Lund** (J. Tennvall, MD) Correspondence to Dr Per Hall.

TABLE I—CHARACTERISTICS OF PATIENTS EXPOSED TO ^{131}I ACCORDING TO DIAGNOSTIC OR THERAPEUTIC PROCEDURE

Characteristic	Diagnostic procedure	Treatment for hyperthyroidism	Treatment for thyroid cancer	All patients
Number of patients	36 326 (77%)	9860 (21%)	802 (2%)	46 988 (100%)
F/M (%)	79/21	82 18	73 27	79 21
Mean (range) age at exposure (yr)	44 (1–75)	57 (13–75)	51 (11–75)	47 (1–75)
Mean number of ^{131}I administrations	1·3	1·6	1·4	1·4
Mean total administered activity of ^{131}I (MBq)	1·9	505	4532	185
Mean 24 h thyroid uptake (%)	40	57	13	43
Mean (median) dose to bone marrow (mGy)	0·19 (0·11)	48 (35)	251 (182)	14 (0·18)
Dose range (mGy)	0·01–4·44	1–810	26–2226	0·01–2226
Mean (range) follow-up (yr)	22 (2–37)	17 (2–37)	16 (2–37)	21 (2–37)

studies are lack of dosimetry data or use of mean organ doses.

Here we report individual bone marrow doses calculated for the first time among nearly 47 000 individuals for abroad range of ^{131}I doses indicated for diagnostic or therapeutic reasons. Our purpose was to provide insights into the possible leukaemic risk associated with protracted radiation exposure.

Patients and methods

Patient characteristics

Patients were recruited from seven departments of oncology and radiotherapy in Sweden.[6,8,9] Information abstracted from the medical records included: name, sex, date of birth, identification number, administered activity of ^{131}I, number of examinations/treatments, 24 h thyroid uptake of ^{131}I, and reason for the administration. For patients given ^{131}I for therapeutic reasons, information on disease and other treatment(s) was also abstracted.

The patients had been given ^{131}I between 1950 and 1975, were under 75 years of age when exposed to ^{131}I, and were alive 2 or more years later. Patients receiving radiotherapy before ^{131}I were excluded. 46 988 patients (80% female, 20% male) met the selection criteria.

Personal identification numbers not available in the medical records were sought through local parishes and population registers. This unique identification number consists of six digits for year, month, and day of birth, supplemented by a four-digit registration number, and facilitates linkage with various population registers in Sweden.

^{131}I was given to 36326 patients for diagnostic between 1950 and 1969 and therapeutic doses of ^{131}I were given to 9860 patients with hyperthyroidism and to 802 thyroid cancer patients (table I). The mean age at the time of ^{131}I exposure was 47 years (range 1-75) for the combined study group. 34% were younger than 40 years at exposure, 46% were aged 40-60 and 20% were over 60.

Dosimetry

The average number of examinations in the diagnostic cohort was 1·3, the average administered of ^{131}I 1·9 MBq (1 MBq = 378 μ Ci), and the mean thyroid uptake was 40% (table I). Corresponding figures for the hyperthyroid cohort were 1·6, 505 MBq, and 57%, respectively, and for the thyroid cancer patients, 1·4, 4532 MBq, and 13%.

The radiation dose to a specific organ from ^{131}I depends mainly on the amount of ^{131}I circulating in the blood, which has not been concentrated in the thyroid (or, for thyroid cancer, in a metastasis); on the quantity of organically bound ^{131}I released as thyroid hormones; on the local accumulation of ^{131}I in iodine-concentrating tissue (e.g. thyroid gland, salivary glands, gastrointestinal tract, urinary tract); and on the radiation received from ^{131}I concentrated in nearby organs.[5] The bone-marrow absorbed dose derives mainly from organically bound ^{131}I and circulating ^{131}I, which implies that the absorbed dose for a given activity of ^{131}I increases with increasing 24 h thyroid uptake.

To estimate bone marrow doses for individual patients, the total administered ^{131}I activity, 24 h thyroid uptake, and ICRP tables were used.[11] 24 h uptake was known for practically all patients except those with thyroid cancer (39% missing), and for these, uptakes of 5% were assumed if a total thyroidectomy had been performed, and 25% if a subtotal thyroidectomy had been done.

Statistical procedure

The risk of radiation-induced leukaemia was estimated by comparing the number of leukaemias in the exposed population with the number expected in the Swedish population as a whole. Observed numbers of leukaemias were identified by matching the cohort with the Swedish Cancer Register (SCR) for the period 1958-87. The nationwide SCR was started in 1958 and receives reports on newly diagnosed cancers from clinicians, pathologists, and cytologists, and more than 96% of all cancers are reported.[12] Leukaemias found before exposure and within 2 years of exposure were excluded since it is unlikely that they were induced by ^{131}I. Person-years at risk (PYR) were computed from Jan 1, 1958, or 2 years after the date of first exposure if later than this date, until death or Dec 31, 1987.[13] The expected numbers of leukaemias were calculated by multiplying the sex, age, and calendar-year-specific PYR with the corresponding incidence rates based on data from rhe SCR.

In the univariate analyses, the observed number of leukaemias was assumed to be distributed as a Poisson variable and standardised incidence ratios (SIRs) were calculated as the ratio of observed to expected numbers. In the multivariate analyses of the

TABLE II—OBSERVED NUMBER OF LEUKAEMIAS, SIR, AND 95% CI IN RELATION TO SEX, EXPOSURE GROUP, ABSORBED DOSE TO BONE MARROW, AND TYPE OF LEUKAEMIA

Subgroup	Non-CLL			CCL			All leukaemias		
	No	SIR	95% CI	No	SIR	95% CI	No	SIR	95% CI
Total	130	1·09	0·91–1·29	65	1·08	0·84–1·38	195	1·09	0·94–1·25
Females	104	1·13	0·92–1·37	43	1·08	0·78–1·45	147	1·11	0·94–1·31
Males	26	0·94	0·62–1·38	22	1·09	0·68–1·65	48	1·01	0·74–1·33
Diagnostic procedure	103	1·17	0·95–1·41	49	1·14	0·84–1·50	152	1·16	0·98–1·36
Treatment for hyperthyroidism	25	0·85	0·55–1·25	12	0·75	0·39–1·30	37	0·81	0·57–1·12
Treatment for thyroid cancer	2	1·22	0·15–4·41	4	4·49	1·22–11·51	6	2·37	0·87–5·16
Dose to bone marrow (mGy) (and mean dose)									
0·00–0·01 (0·009)	10	1·28	0·62–2·36	2	0·53	0·06–1·90	12	1·04	0·53–1·81
0·02–0·10 (0·058)	31	1·01	0·69–1·44	17	1·15	0·67–1·83	48	1·06	0·78–1·40
0·11–10 (3·5)	62	1·23	0·94–1·58	30	1·22	0·82–1·74	92	1·23	0·99–1·50
11–100 (39)	23	0·85	0·54–1·28	9	0·62	0·28–1·17	32	0·77	0·53–1·09
>100 (221)	4	1·04	0·28–2·67	7	3·17	1·27–6·53	11	1·82	0·91–3·26

TABLE III—OBSERVED NUMBER OF LEUKAEMIAS, SIR, AND 95% CI IN RELATION TO AGE AT EXPOSURE, YEARS AFTER EXPOSURE, AND TYPE OF LEUKAEMIA

Subgroup	Non-CLL			CCL			All leukaemias		
	No	SIR	95% CI	No	SIR	95% CI	No	SIR	95% CI
Age at exposure (yr)									
< 40	19	1·07	0·64–1·67	5	1·03	0·34–2·41	24	1·06	0·68–1·58
40–60	78	1·17	0·92–1·45	39	1·18	0·84–1·62	117	1·17	0·97–1·40
> 60	33	0·93	0·64–1·31	21	0·93	0·58–1·42	54	0·93	0·70–1·22
Years after exposure									
2–9	38	0·95	0·67–1·30	13	0·71	0·38–1·21	51	0·87	0·65–1·14
10–19	63	1·29	0·99–1·65	30	1·22	0·83–1·75	93	1·27	1·02–1·55
> 20	29	0·96	0·64–1·37	22	1·26	0·79–1·90	51	1·07	0·80–1·41

leukaemia incidence, Poisson regression models were used to study the influence of ^{131}I subcohort, sex, absorbed dose, age at exposure, and time since exposure. Estimates of relative risk (RR) were computed with maximum-likelihood methods using a computer program for general linear regression models.[14] Cofidence intervals (CI) were calculated on the basis of standard large-sample Statistical theory.

Results

Dosimetry

The mean absorbed dose to the bone marrow was 14 mGy (median 0·18, range 0·01-2·226; table I). 7% (n = 3470) of patients received <=0·01 mGy, 29% (n = 13 463) 0·02-0·10 mGy, 40% (n = 19 071) 0·11-1·0 mGy, 1% (n = 470) 1·1-10 mGy, 19% (n = 9023) 11-100 mGy, and 3% (n = 1491 >100 mGy. Only 22 patients received more than 1Gy to the bone marrow. In the analyses, patients receiving 0·11-10 mGy were grouped together.

Risk estimates

The average follow-up was 21 years (range 2-37; table I). 12% of patients were followed up for less than 10 years and 47% for more than 20 years. PYR numbered 943 944 (females 766 143, males 179 801).

218 leukaemias were found; the 7 from before and the 16 developing within 2 years of the ^{131}I administration were excluded. The SIR for all leukaemias was 1·9 (95% CI 0·94-125; table II). It was slightly higher for women (1·11) than for men (1·01). The highest (SIR = 1·82) was seen among patients receiving >100 mGy but this was not statistically significant. However, this risk was almost entirely due to excesses of chronic lymphatic leukaemia (CLL), one of the few malignant conditions that so far have nor been linked to radiation exposure. No apparent pattern in leukaemia risk was seen for age at exposure or time since exposure (table III). The highest risk was observed 10-19 years after exposure (SIR = 1·27), and was similar for CLL (SIR = 1·22) and non-CLL (SIR = 1·29). For patients under 40 at exposure, the SIR for leukaemia was 1·03 and 1·07 for CLL and non-CLL, respectively.

In the subgroup analyses, significantly increased risks were seen only for CLL and only among thyroid cancer patients (SIR = 4·49; n = 4) and among those who received more than 100 mGy (SIR= 3·17; table II). No significant results or patterns were apparent for non-CLL.

To avoid the possibility that the general population might not be an appropriate comparison for this cohort, multivariate analyses were done with the lowest dose group (<0·01 mGy) as referent (table IV). The internal comparisons were adjusted for sex, age, and calendar year. The results did not differ from those obtained with the population-based RR.

Discussion

The administration of ^{131}I to nearly 47 000 patients did not influence the subsequent risk of leukaemia. The risk of CLL, a malignancy that has not been associated with ionising radiation, was similar to that of non-CCL. Nor was there evidence for a higher risk among the young (under 40) or in the years 2-9 after exposure, as would have been anticipated from previous studies of radiogenic leukaemia.[1] The absence of both a typical temporal pattern for radiogenic leukaemia and a dose-response relation, coupled with similar risks for CLL and non-CLL, indicate that leukaemia was rarely induced by ^{131}I in our study population.

Among Japanese atomic bomb survivors 202 leukaemias were recorded from 1950 to 1985, and the mortality was significantly increased for those receiving >400 mGy to the bone marrow.[15] A linear-quadratic function best described the dose-response relation. Increased risks have also been found in patients treated with X rays for ankylosing spondylitis,[16] to stop uterine bleeding,[17] in Israeli children mated with cranial irradiation for ringworm of the scalp,[18] and in patients exposed to the thorium contrast agent, Thorotrast.[19] A small excess of leukaemia was found in more than 200 000 women treated with high-dose radiotherapy for cervical cancer, despite a bone-marrow dose of 3-15 Gy.[20] This was explained by the local cell-killing effect of radiation.

Pioneering radiologists were at increased risk of leukaemia after low-dose exposure for many years, but the lack of radiation dose estimates limits the value of these studies.[21-23] Studies of workers in the nuclear industry have been generally non-informative on leukaemia risks, largely because of the relatively low whole-body doses. Wing et al[24] observed an increased risk of leukaemia after occupational

TABLE IV—RISK OF LEUKAEMIA, ADJUSTED FOR SEX, AGE AT EXPOSURE, AND CALENDAR YEAR IN RELATION TO ABSORBED DOSE TO BONE MARROW, CALCULATED BY POISSON REGRESSION MODELS

Dose to bone marrow (mGy) (and mean dose)	Non-CLL			CCL			All leukaemias		
	No	RR	95% CI	No	RR	95% CI	No	RR	95% CI
0·00–0·01 (0·009)	10	1·00	. .	2	1·00	. .	12	1·00	. .
0·02–0·10 (0·058)	31	0·08	0·39–1·62	17	2·22	0·52–9·63	48	1·03	0·55–1·82
0·11–10 (3·5)	62	1·01	0·52–1·98	30	2·54	0·61–10·63	92	1·27	0·70–2·32
11–100 (39)	23	0·68	0·32–1·43	9	1·17	0·25–5·41	32	0·75	0·38–1·46
> 100 (221)	4	0·82	0·26–2·64	7	6·49	1·34–31·33	11	1·82	0·80–4·15

exposure at one national laboratory. The association was, however, inversely related to radiation dose. The difficulty in estimating doses retrospectively from environmental contamination also adds caution to interpreting the associations as causal.

Several studies of patients treated with ^{131}I have been published but give little evidence of a carcinogenic effect of the isotope. In three studies of thyroid cancer patients treated with high activities of ^{131}I, increased risks of leukaemia were found, but the numbers of leukaemias were small, (2, 3, and 4 cases, respectively[4-6]). Saenger et al.[10] reported similar increased risks for leukaemia in hyperthyroid patients treated with ^{131}I (n = 22 000) as in those treated by surgery (n = 14 000).

When risk estimates were calculated in data from the Life Span Study (LSS) of the Japanese atomic bomb survivors, dose, age at expoure, and time since exposure being taken into account, an RR of 1·06 was found.[1] Among patients receiving <100 mGy to the bone marrow, the RR was 104, compared with 1·81 in patients receiving >100 mGy. This should be related to our findings of 1·09 95% CI 0·91-1·30) and 1·04 95% CI 0·28-2·67), respectively. There seems to be a difference in risk between protracted and instantaneous ionising radiation at doses >100 mGy, although the SIR of 1·04 was based on few cases and the Japanese RR of 1·81 lies within the 95% CI for Swedish data.

This absence of a radiation effect in our series is probably due either to the relatively low dose received by active bone marrow from ^{131}I or to a decrease in carcinogenic effect from protracted exposure to low linear energy threshold irradiation. Except for patients treated for thyroid cancer, bone-marrow doses were well under 500 mGy and the power to detect a radiation risk at such low exposure is accordingly low. Evidence from animal experiments generally indicates a lowering of cancer risk when exposures are prolonged over time, perhaps related to cellular repair mechanisms having more time to correct damaged DNA.[1] ^{131}I is predominantly (90%) a beta-emitter, whereas existing risk estimates are based mainly on X gamma rays. The relative biological effectiveness for these types of irradiation is similar, and it is therefore more likely that the difference in dose rate explains the effect on the risk of a subsequent leukaemia.

There is always a reason why some patients are exposed to ^{131}I and others not and this could have biased the results. The comparisons with the general population might not be strictly appropriate, and an internal comparison group was therefore used. Since the findings were similar, it is unlikely that the patient selected introduces a serious bias, something which adds credibility to our results.

Results from the present cohort have previously been published but without individual organ doses,[6,8,9] Very few epidemiological cohort studies concerning radiation-induced cancer have been able to calculate individual organ doses for the whole study population. The lack of dosimetry or use of mean organ doses will introduce an error especially for large inter-individual differences in dose.

Despite large numbers of ^{131}I exposed subjects, estimates of bone marrow dose, and long-term and nearly complete follow-up of the population, no radiation effect was detected. The results of our study should be reassuring to patients given ^{131}I for diagnostic or therapeutic reasons and also to most **of those exposed to fall-out from the** Chernobyl accident. The average individual total body dose in Europe has been calculated to 1·5 mGy for the first 50 years after the accidentt,[25] a dose that was not associated with an increased risk of leukaemia in our study.

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